The John Snow Project

EDITORIAL

COVID-19: A NEW DISEASE PARADIGM

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What if SARS-CoV-2 continues to infect us even after the initial symptoms fade?

A recent study from the University of California San Francisco (UCSF) used advanced imaging techniques to identify persistent T lymphocyte activation in many parts of the body up to 2.5 years after acute SARS-CoV-2 infection. The team found T cell activation in the brain stem, spinal cord, bone marrow, nasopharyngeal and hilar lymphoid tissue, cardiopulmonary tissues, and gut wall. This activation was significantly higher than pre-pandemic controls. T cell activation in the spinal cord and gut wall was associated with the presence of Long COVID symptoms, but T cell activation was found even in those who were not experiencing any Long COVID symptoms at the time of imaging. T cell activation in the lung was associated with noticeably higher pulmonary symptoms. The team also found SARS-CoV-2 RNA in rectal tissue in all symptomatic participants, ranging from 158 to 676 days following initial infection, suggesting that viral persistence could be associated with long-term immunological dysfunction[1].

This study adds to numerous others that have found evidence of persistent infection months after acute illness[2-8]. A recent review of viral persistence in the context of Long COVID outlined the evidence that points towards ongoing infection or viral, protein or RNA replication[9], but evidence of persistence is not limited to people who are exhibiting symptoms of Long COVID. One study found persistent infection in the tonsils of 25% of asymptomatic children[2], while other studies have found evidence of persistent infection of children in other organs[8]. SARS-CoV-2 proteins, including spike, have been found in Long COVID and convalescent blood up to 12 months after initial infection[10]. One study found spike protein in the plasma of 64% of Long COVID patients and 29% of convalescent controls. This protein is likely derived from persistent SARS-CoV-2 in tissue reservoir sites and "leaks" into the blood where it can be measured[11].

The UCSF imaging study also adds to those studies that have found persistent T cell activation. One study[12], published as a pre-print, found an association between activation of a specific T cell subtype and the propensity to test positive after apparent recovery. In another study, the same T cell subtype was found to be elevated 12 months after acute infection in subjects whether they had suffered mild or severe illness, with no reduction in activation between the

6-month and 12-month post-infection marks[13]. Expanded T cell populations in the pharyngeal lymphoid tissue of children weeks or months after infection was observed in another study[14], and activation markers CD38, HLADR, and Ki67 were similarly expressed months after acute infection in people with and without Long COVID according to another study[15] out of UCSF. Immune CD8+ T cell activation was observed in plasma of convalescent patients irrespective of developing Long COVID, with participant CD4/CD8 ratios remaining low 6 months after COVID-19 diagnosis. Higher levels of plasma IgA against SARS-CoV-2 S and N proteins and redistribution of CD8+ T cells expressing the mucosal homing β7 Integrin were identified in Long COVID and some convalescent participants, suggesting the persistence of SARS-CoV-2 in mucosal tissues[16].

If UCSF imaging data are verified then they suggest that everyone who has had COVID-19 might have been subjected to these effects and that ongoing immune activation might be a common feature of all COVID-19 infections regardless of perceived Long COVID status. A possible explanation of persistent activation would be persistent infection, now evidenced in a number of SARS-CoV-2 studies, and seen in other viral infections such as human cytomegalovirus[17-19] and Epstein-Barr virus[20,21]. In immunological terms, with regard to the activation of T lymphocytes, the UCSF study suggests people who have recovered from COVID-19 might be on the same spectrum as people with symptomatic Long COVID, and just as it is possible to have asymptomatic acute COVID-19, it is possible to have asymptomatic or paucisymptomatic Long COVID where the biological effects are experienced less keenly and are controlled sufficiently by the immune system so as not to manifest symptoms or to manifest them mildly.

Persistent infection is seen in a variety of conditions that drive persistent T cell activation[22-30], and this persistent activation is associated with a variety of clinical and immunological outcomes[31-41], making it difficult to say with any certainty what will happen due to ongoing immune activation even if experienced asymptomatically. It could have a minimal impact on human health and affect only a small proportion of the population long-term. It could cause more serious harms, such as increases in neurodegenerative disease,

autoimmunity, more rapid immunosenescence, or it could cause specific time-limited or longer-term immune deficiency for a small or large proportion of the population.

There is the possibility some people with symptomatic Long COVID experience a loss of unactivated naïve B and T cells at 8 months post infection[42], and whether this finding is related to increased cell turnover due to heightened immune activation needs further study. A follow up study to the one that showed the loss of unactivated naïve B and T cells at 8 months[42] found immune reconstitution in the same cohort at 24 months[43], suggesting some degree of recovery, but, interestingly, although many of the differences between the two groups resolved, the matched controls and Long COVID cohort in the study showed the same absolute elevated markers of exhaustion at 24 months compared with 12 months, suggesting everyone infected with SARS-CoV-2 in this study experienced increased T cell activation as a result of infection.

An analogy for what we're seeing may be found in Hepatitis B (HBV) where people with chronic HBV go through four phases of infection; an immune tolerant phase when host immunity is weak and viral load is high, an immune active phase when host immunity is strong and viral load decreases, an immune control phase during which host immunity can control the viral load, and a reactivation phase during which weakened host immunity can cause a loss of control of the viral load[44]. In the case of HBV, T cell activation and exhaustion constrains effective viral clearance[45,46]. Treatment of HBV can restore T cell phenotypes and might be used as a predictive measure for the effectiveness of the treatment[47]. Lessons from Hepatitis B and HIV suggest we need effective biomarkers for the COVID-19 host immune response and the location and amount of any persistent SARS-CoV-2 virus or RNA. It may be that levels of T cell activation with CD38 and HLA-DR expression combined with other specific immune responses can be used to develop an effective host biomarker[13,48], and further research is needed to develop methods to identify the amount and location of persistent virus suggested by persistent peripheral T cell activation[1] and evidenced numerous studies of adults and children[2-11, 12-16].

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A broad range of immunological outcomes would seem to be on the table based on the existing study of the immunology of Long COVID[49], from minimal to serious impact to human health. Although T cell activation has been evidenced in acute and Long COVID, it might not be the root cause of the immunological issues we have been seeing in the affected population, and, as a virus that depletes dendritic cells[50], infects macrophages[51], platelets[52], T lymphocytes[2,53,54], monocytes[55], megakaryocytes[52,56,57] bone marrow[7,57], and makes long-term alterations to the innate immune system[58,59], SARS-CoV-2 may have complex, multi-faceted impacts on the immune system that will only be fully elucidated over time.

The issue we face is we may not know the full extent of harm until it is too late to remedy it, and in the context of a virus that has infected most of the global population, including children, and continues to circulate and reinfect, this would seem to be an unacceptable risk. Governments, particularly those in high income countries, need to take the lead and engage in an urgent effort to develop treatments that target any persistent viral reservoirs in the body, concurrent with research efforts into developing a better understanding of Long COVID and the roles of viral persistence and immune dysfunction in the condition. We cannot risk waiting for a complete understanding before beginning urgent efforts to clear any viral reservoirs that may exist.

In light of the accumulating evidence, we propose a new paradigm for COVID-19:

COVID-19 is a disease that has an acute and chronic phase. Both phases can be asymptomatic or symptomatic, and the severity and nature of symptoms in either phase depends on the host immune response, viral inoculum and location of infection. In the chronic phase, commonly known as Long COVID, many more people than those who exhibit symptoms of Long COVID, or perhaps everyone who has been infected by COVID-19, is on the same spectrum of T cell activation and may share as yet undiscovered characteristics of viral persistence or immune dysfunction, regardless of whether they

experience Long COVID symptoms or not, and the experience of those symptoms, which may be associated with further immune perturbation on reinfection, may be related to the location and/or quantity of viral RNA/protein /replicating virus in persistent reservoirs.

This paradigm makes COVID-19 in both its acute and chronic phase a global concern and a problem that needs to be solved urgently. It means the 'othering' of Long COVID is not an acceptable government or public health response, and recognizes that anyone and everyone might suffer from the condition on first exposure. And the probability to move to symptomatic Long COVID may be enhanced with multiple infections where viral persistence might be exacerbated. The work cited here suggests many more people, and perhaps everyone, who has been infected with SARS-CoV-2 may already be experiencing the same heightened T cell activation as those suffering Long COVID with the only difference being symptom expression.

The US Department of Health and Human Services and the World Health Organization have recently warned [60,61] that we risk adding to the number of people suffering Long COVID with each reinfection, but under the new paradigm it might be that we are adding a sufficient amount of virus, or infection in new parts of the body to tip more people into symptomatic Long COVID with all that might entail [49]. The burden of the condition is already significant [62] and is being felt around the world [63].

We have recently surveyed countries and territories that have published specific guidelines on the prevention of Long COVID [64]. In the context of a new paradigm, prevention of reinfection becomes more urgent, and measures to curtail transmission need to go hand in hand with an unprecedented push to research treatments to neutralize the virus in any persistent reservoirs, alongside a better understanding of the long-term immunology of COVID-19. As part of this better understanding, we urge governments to provide more funding for research into the long-term immunological impacts of COVID-19 in children.

We believe governments need to set the prevention of transmission of SARS-CoV-2 as an objective. They should invest in this objective and normalize non-pharmaceutical interventions against SARS-CoV-2 transmission and explain to the general public why they are doing so, and organizations and individuals should do more to protect themselves from COVID-19 and prevent transmission of SARS-CoV-2. We support the Vaccines-plus and Delphi Consensus recommendations [65,66] as viable models for achieving reduction in transmission with minimal social and economic disruption until work on a sterilizing vaccine and effective treatments of any persistent reservoirs is concluded.

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The public health, social, and economic costs of Long COVID are already too high, so there is no downside to the recommended action. Much of the potential harm of Long COVID is still unknown as it may manifest years or decades later. If there is no further long-term harm to be discovered, preventing the harms we already know about is sufficient cause for action, but if we later discover long-term harms that are on the more serious end of the spectrum of possible outcomes, we will be very glad we acted sooner rather than later.

Click here for information on how to reduce your risk.

References

1. Multimodal Molecular Imaging Reveals Tissue-Based T cell Activation and Viral RNA Persistence for Up to 2 Years Following COVID-19
https://www.medrxiv.org/content/10.1101/2023.07.27.23293177v1

2. Asymptomatic SARS-CoV-2 infection in children's tonsils
https://www.sciencedirect.com/science/article/pii/S1808869422001392

3. Persistence of SARS-CoV2 RNA in lung tissue after mild COVID-19
https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00240-X/fulltext

4. Evolution of antibody immunity to SARS-CoV-2
https://pubmed.ncbi.nlm.nih.gov/33461210/

5. Gastrointestinal symptoms and fecal shedding of SARS-CoV-2 RNA suggest prolonged gastrointestinal infection
https://www.cell.com/med/fulltext/S2666-6340(22)00167-2

6. SARS-CoV-2 infection and persistence in the human body and brain at autopsy
https://www.nature.com/articles/s41586-022-05542-y

7. SARS-CoV-2 Spike Protein Accumulation in the Skull-Meninges-Brain Axis: Potential Implications for Long-Term Neurological Complications in post-COVID-19
https://www.biorxiv.org/content/10.1101/2023.04.04.535604v1

8. Viral persistence in children infected with SARS-CoV-2: current evidence and future research strategies
https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(23)00115-5/fulltext

9. SARS-CoV-2 reservoir in post-acute sequelae of COVID-19 (PASC)
https://www.nature.com/articles/s41590-023-01601-2

10. Persistent circulation of soluble and extracellular vesicle-linked Spike protein in individuals with postacute sequelae of COVID-19
https://pubmed.ncbi.nlm.nih.gov/36756925/

11. Persistent Circulating Severe Acute Respiratory Syndrome Coronavirus 2 Spike Is Associated With Post-acute Coronavirus Disease 2019 Sequelae
https://pubmed.ncbi.nlm.nih.gov/36052466/

12. Analysis of differences in lymphocyte subsets and CD4+ T cells immune activation between re-detectable positive and non-re-detectable positive COVID-19 convalescent patients
https://www.researchsquare.com/article/rs-1896362/v1

13. T-cell recovery and evidence of persistent immune activation 12 months after severe COVID-19
https://onlinelibrary.wiley.com/doi/full/10.1111/all.15372

14. Adaptive immune responses to SARS-CoV-2 persist in the pharyngeal lymphoid tissue of children
https://www.nature.com/articles/s41590-022-01367-z

15. Long COVID manifests with T cell dysregulation, inflammation, and an uncoordinated adaptive immune response to SARS-CoV-2
https://www.biorxiv.org/content/10.1101/2023.02.09.527892v2.full

16. Post-acute sequelae of COVID-19 is characterized by diminished peripheral CD8+β7 integrin+ T cells and anti-SARS-CoV-2 IgA response

anti-SARS-CoV-2 IgA response
https://www.nature.com/articles/s41467-023-37368-1

17. Human cytomegalovirus persistence
https://onlinelibrary.wiley.com/doi/full/10.1111/j.1462-5822.2012.01774.x

18. Human cytomegalovirus infection and atherothrombosis
https://link.springer.com/article/10.1007/s11239-011-0662-x

19. Tissue reservoirs of antiviral T cell immunity in persistent human CMV infection
https://rupress.org/jem/article/214/3/651/42176/Tissue-reservoirs-of-antiviral-T-cell-immunity-in

20. The pathogenesis of Epstein–Barr virus persistent infection
https://www.sciencedirect.com/science/article/abs/pii/S1879625713000576

21. Regulatory T cell activity in primary and persistent Epstein–Barr virus infection
https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.21445

22. Acute vs. Chronic Hepatitis C: Understanding Your Treatment Options
https://www.healthline.com/health/hepatitis-c/acute-vs-chronic

23. Hepatitis B
https://my.clevelandclinic.org/health/diseases/4246-hepatitis-b

24. Hepatitis C virus clearance, reinfection, and persistence, with insights from studies of injecting drug users: towards a vaccine
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3608418/

25. Age-related immune clearance of hepatitis B virus infection requires the establishment of gut microbiota
https://www.pnas.org/doi/10.1073/pnas.1424775112

26. Clearance of hepatitis C virus is associated with early and potent but narrowly-directed, Envelope-specific antibodies
https://www.nature.com/articles/s41598-019-49454-w

27. Malaria drives T cells to exhaustion
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4034037/

28. Tissue reservoirs of antiviral T cell immunity in persistent human CMV infection
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5339671/

29. Persistent T Cell Repertoire Perturbation and T Cell Activation in HIV After Long Term Treatment
https://pubmed.ncbi.nlm.nih.gov/33732256/

30. HIV-1 replication activates CD4+ T cells with specificities for persistent herpes viruses
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3377320/

31. T-cell exhaustion: characteristics, causes and conversion
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2842494/

32. Lessons from the study of T-cell differentiation in persistent human virus infection
https://www.sciencedirect.com/science/article/abs/pii/S1044532304000259

33. T cell exhaustion during persistent viral infections

https://www.sciencedirect.com/science/article/pii/S0042682214005820

34. Mechanisms Underlying T Cell Immunosenescence: Aging and Cytomegalovirus Infection
https://www.frontiersin.org/articles/10.3389/fmicb.2016.02111/full

35. Human T cell immunosenescence and inflammation in aging
https://jlb.onlinelibrary.wiley.com/doi/full/10.1189/jlb.3RI0716-335R

36. The role of oxidative and inflammatory stress and persistent viral infections in immunosenescence
https://www.sciencedirect.com/science/article/abs/pii/S004763741630001X

37. Not-so-opposite ends of the spectrum: CD8+ T cell dysfunction across chronic infection, cancer and autoimmunity
https://www.nature.com/articles/s41590-021-00949-7

38. Metabolic exhaustion in infection, cancer and autoimmunity
https://www.nature.com/articles/s41590-018-0045-y

39. The role of the adaptive immune system and T cell dysfunction in neurodegenerative diseases
https://link.springer.com/article/10.1186/s12974-022-02605-9

40. Alzheimer's Disease-Associated β-Amyloid Is Rapidly Seeded by Herpesviridae to Protect against Brain Infection
https://pubmed.ncbi.nlm.nih.gov/30001512/

41. Association of COVID-19 with New-Onset Alzheimer's Disease
https://pubmed.ncbi.nlm.nih.gov/35912749/

42. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection
https://www.nature.com/articles/s41590-021-01113-x

43. Improvement of immune dysregulation and health-related quality of life in individuals with long COVID at 24-months following SARS-CoV-2 infection
https://www.medrxiv.org/content/10.1101/2023.08.27.23294704v1

44. World Health Organization Training on Screening, Diagnosis and Treatment of Hepatitis B & C
https://www.who.int/docs/default-source/searo/hiv-hepatitis/training-modules/07-hbv-natural-history.pdf?sfvrsn=520b7c01_2

45. Unraveling the Multifaceted Nature of CD8 T Cell Exhaustion Provides the Molecular Basis for Therapeutic T Cell Reconstitution in Chronic Hepatitis B and C
https://www.mdpi.com/2073-4409/10/10/2563

46. Peripheral natural killer cells in chronic hepatitis B patients display multiple molecular features of T cell exhaustion
https://elifesciences.org/articles/60095

47. Longitudinal characterization of phenotypic profile of T cells in chronic hepatitis B identifies immune markers associated with HBsAg loss
https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00257-7/fulltext

48. Identification of Distinct Immune Cell Subsets Associated With Asymptomatic Infection, Disease Severity, and Viral Persistence in COVID-19 Patients
https://www.frontiersin.org/articles/10.3389/fimmu.2022.812514/full

49. The immunology of long COVID
https://www.nature.com/articles/s41577-023-00904-7

50. Dendritic cell deficiencies persist seven months after SARS-CoV-2 infection
https://www.nature.com/articles/s41423-021-00728-2

51. Circuits between infected macrophages and T cells in SARS-CoV-2 pneumonia
https://www.nature.com/articles/s41586-020-03148-w

52. Infection of lung megakaryocytes and platelets by SARS-CoV-2 anticipate fatal COVID-19
https://link.springer.com/article/10.1007/s00018-022-04318-x

53. SARS-CoV-2 uses CD4 to infect T helper lymphocytes
https://elifesciences.org/articles/84790

54. ACE2-independent infection of T lymphocytes by SARS-CoV-2
https://www.nature.com/articles/s41392-022-00919-x

55. FcγR-mediated SARS-CoV-2 infection of monocytes activates inflammation
https://www.nature.com/articles/s41586-022-04702-4

56. Circulating SARS-CoV-2+ megakaryocytes are associated with severe viral infection in COVID-19
https://www.sciencedirect.com/science/article/pii/S2473952923001404

57. Megakaryocyte infection by SARS-CoV-2 drives the formation of pathogenic afucosylated IgG antibodies in mice

58. Epigenetic memory of coronavirus infection in innate immune cells and their progenitors
https://www.cell.com/cell/fulltext/S0092-8674(23)00796-1

59. Severe COVID-19 may lead to long-term innate immune system changes
https://www.nih.gov/news-events/news-releases/severe-covid-19-may-lead-long-term-innate-immune-system-changes
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60. US Department of Health and Human Services Advice on Avoiding Long Covid
https://johnsnowproject.org/primers/hhs-advice-on-avoiding-long-covid/

61. World Health Organization Advice to Protect Against Long Covid
https://johnsnowproject.org/primers/who-advice-to-protect-against-long-covid/

62. Long COVID: major findings, mechanisms and recommendations
https://www.nature.com/articles/s41579-022-00846-2

63. Long COVID in low-income and middle-income countries: the hidden public health crisis
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)01685-9/fulltext

64. International Guidance on Preventing Long Covid
https://johnsnowproject.org/primers/international-guidance-on-preventing-long-covid/

65. Covid-19: An urgent call for global “vaccines-plus” action
https://www.bmj.com/content/376/bmj.o1

66. A multinational Delphi consensus to end the COVID-19 public health threat

66. A multinational Delphi consensus to end the COVID-19 public health threat
https://www.nature.com/articles/s41586-022-05398-2